

**Application No. 09/743,577**

**Art Unit 1616**

**Submission with RCE**

**Response to Final Office Action and Advisory Actions**

**REMARKS**

Applicant herein requests an Interview with the Examiner, and further requests such Interview take place before issuance of the first Office Action. Applicant also requests that the first Office Action be non-Final.

A Request for Continued Examination is being concurrently filed with this Submission. The present Submission fully complies with M.P.E.P. § 706.07(h)(II).

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the claims.

In the present reply, claims 2, 3, 6, 8, 10, and 11 have been amended. Thus, claims 2-13, 17-19, and 22-40 are pending and are ready for further action on the merits. No new matter has been added by way of the above amendments. These claims have merely been amended based on a suggestion by the Examiner to make the claims more clear. Further, the changes to claims 6 and 8 are merely editorial in nature. These amendments are non-narrowing in scope. By changing these terms in order to clarify the claimed invention, Applicant is in no way conceding any limitations with respect to the interpretation of the claims under the Doctrine of Equivalents.

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Based upon the above considerations, entry of the present amendment is respectfully requested.

Applicant notes that the replies of July 8, 2004 and August 9, 2004, have not been entered. The present reply is in response to the Final Office Action of January 8, 2004.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

***Issues Under 35 U.S.C. § 103(a)***

Claims 2-9, 11, 13, 17-19, 22-35, and 38-40 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hersh '791 (U.S. Patent No. 5,667,791) (as stated at pages 2-5 of the Final Office Action of January 8, 2004).

Also, claims 2, 6, 7, 9-12, 17-19, 28-31 and 34-40 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hillebrand '500 (U.S. Patent No. 5,296,500) (see starting at the bottom of page 5 of the Final Office Action).

Applicant respectfully traverses, and reconsideration and withdrawal of these rejections are respectfully requested based on the following.

**The Present Invention and the Unexpected Features Thereof**

The present invention, as recited in claim 2, relates to a preparation for topical application comprising the following components:

- (a) at least one salt selected from alkali metal salts, alkaline earth metal salts and other minerals,
- (b) at least one individual amino acid,
- (c) zinc oxide and/or an inorganic peroxide, and
- (d) at least one secondary plant substance selected from the group consisting of carotenoids, phytosterols, saponins, polyphenols, flavonoids, terpenes, phytoestrogens, sulfides, phytin acid, dietary fibers and combinations thereof.

As recited in claim 3, the instant invention further comprises

- (e) at least one polyunsaturated fatty acid of vegetable sources in addition to the components that are in claim 2.

Applicant has found that the combination of zinc oxide and/or inorganic peroxides improves the microcirculation in the cell. This improvement can be both visually and biometrically shown. The improvement is further increased by the use of at least one salt and at least one secondary plant substance.

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Disclosure of Hersh '791

Hersh '791 discloses a composition of glutathione and selenomethionine in a topical carrier and method of using the composition to reduce and repair x-ray radiation-induced skin damage.

Hersh '791 fails to disclose a composition containing at least one individual amino acid.

Disclosure of Hillebrand '500

Hillebrand '500 discloses a method for regulating wrinkles and/or atrophy in mammalian skin comprising treating the skin with a safe and effective amount of the amino acid derivative N-acetyl-L-cysteine and/or a derivative thereof.

Hillebrand '500 fails to disclose at least one individual amino acid.

Removal of the Rejection in view of Hersh '791

Applicant respectfully points out that neither Hersh '791 nor Hillebrand '500 discloses at least one individual amino acid.

Applicant submits that amino acids are carboxylic acids having one or more amino groups (-NH<sub>2</sub>) in the molecule. In the technical field of the present invention, amino acids are divided into essential, semi-essential and non-essential amino acids. The about

20 different  $\alpha$ -amino acids found in proteins are rather simple organic compounds having the general structure  $R-CH(NH_2)-COOH$ , in which an amino group and a side-chain (R) are attached alpha to the carboxyl functionality. The R group may be aliphatic, aromatic, or heterocyclic (Applicant respectfully directs the Examiner's attention to reference 2, page 57, paragraph bridging left and right column that was filed with the response of July 8, 2004).

It should be noted that important commonly known amino acids are encoded. The coding of cystine is CysCys (please see reference 3, middle of page 65 that was submitted with the response of July 8, 2004). The person of ordinary skill in the art of the present invention would not regard selenomethionine used in Hersh '791 as a commonly known individual amino acid that is present in unsubstituted form. In the literature considered as belonging to the general knowledge of a person skilled in the art, selenomethionine is described as a "selenium-containing amino acid". It has been further described as a compound, which is (only) comparable with the essential amino acid methionine. In comparison to the amino acid methionine, in selenomethionine, the sulfur atom has been replaced by a selenium atom. That is, this compound contains a metal element and is therefore regarded as an organometallic compound. An organometallic compound is different from an organic amino acid

wherein the substituent R may be aliphatic, aromatic or heterocyclic. Furthermore, it should be emphasized that selenomethionine is a commonly used selenium source for orally administering selenium to mammals. Feeding studies showed that organically bound selenium, such as selenomethionine, is incorporated several times faster into the body tissue than inorganic selenium (see enclosed Ullmann's Encyclopedia of Industrial Chemistry, volume A28, page 465, left column, 4th paragraph). This is also confirmed by Hersh '791 in column 4, lines 13 to 19 and column 8, lines 20 to 25. It should be emphasized that Hersh '791 describes selenomethionine as "selenium-containing seleno amino acid" and not as an individual amino acid (please note column 8, lines 21 and 22). The person of ordinary skill in the art to which the claims are generally addressed interprets the term "amino acid" as it is usually used in the technical field. The inventor of the present invention, who is an expert in the technical field of the present invention, is absolutely sure that every person skilled in the technical field of the present invention would interpret a selenomethione to fall outside of the scope of "at least one individual amino acid" that is usually known in the technical field. The term "amino acid" does not include "amino acid derivatives" or "proteins" or "proteids". This is evidenced by the references that are attached hereto.

Again, the term "amino acid" only comprises well-defined compounds of organic carboxylic acids in free form having unsubstituted amino groups. The selenomethionine used in Hersh '791, therefore, is not included within said term. It should be emphasized again that it is well-known to the person of ordinary skill in the art that selenomethionine is a usual selenium source. This is also confirmed by Hersh '791. In this compound, as mentioned above, the sulfur atom of the essential amino acid methionine has been replaced by the metal atom selenium. Since the essential part of the use of selenomethionine is the provision of selenium, which is also confirmed by Hersh '791, the use of this compound cannot provide any teaching or suggestion with respect to any individual amino acids. In view of this fact, the disclosure of Hersh '791 cannot teach or suggest a composition of the present invention. Thus, the rejection is inapposite. Withdrawal of the rejection over Hersh '791 is warranted and respectfully requested.

Applicant also herein responds to the Advisory Action of September 1, 2004, regarding the term "amino acid derivative". Applicant respectfully submits that the Examiner's position has been adequately rebutted herein. But in the mentioned Advisory Action, the Examiner states that Applicant's position has been rebutted in stating that "a skilled artisan does not consider selenomethione an

amino acid derivative", and further refers to U.S. Patent Nos. 6,094,414 and 5,827,886 (see page 3 of the Advisory Action). In response, Applicant notes the Examiner's position can always be rebutted by submitting the appropriate scientific or technical literature to support Applicant's position of patentability. In particular, citing scientific literature pertaining to the more educated worker in the field (truly scientific articles, such as *Nature* or a biochemistry textbook) and/or related to the more sophisticated technology (versus general knowledge) should more accurately reflect the meaning of amino acids and derivatives thereof. Thus, Applicant submit that the scientific references submitted with Applicant's response of July 8, 2004, is more persuasive than the cited U.S. Patents. Further, the cited U.S. Patents do not rebut Applicant's position as follows.

The cited '414 patent indicates, e.g., in its claim 51 that "the amino acid comprises selenomethionine or selenocysteine". However, this claim refers back to claim 50 that clearly indicates that the organic selenium compound as cited in claim 47 comprises a seleno amino acid. Claims 68 and 110 in the '414 patent also relate back to the previous claim, respectively, which clearly indicates that the selenium compound comprises a seleno amino acid. That is, if one of skill in the art reads the claims cited by the Examiner in the

context of the previous claims to which they refer, it is clear that the term "selenomethionine" is not within the definition of the general term "amino acid," but instead within the term "seleno amino acid". The term "seleno amino acid" generally means an amino acid derivative containing selenium.

With further regard to the '414 patent, Applicant submits that column 18, lines 23-34 indicate that selenium occurs naturally in varying amounts in a wide variety of foods and also is present as an impurity in the natural form of the preferred sulfur-containing amino acids, e.g., with methionine as the compound seleno-methionine. Also in this passage in the '414 patent, there is nothing which clearly indicates that the general term "amino acid" as used by a person skilled in the art includes the amino acid derivative "selenomethionine". This passage in the reference also indicates that in food grade sulfur-containing amino acids, the corresponding seleno-amino acid is normally present due to the similar reactivity of sulfur and selenium. That is, this passage clearly indicates that sulfur is replaced by selenium. Thus, Applicant submits that the '414 patent does not rebut Applicant's position.

With regard to the '886 patent, lines 53 and 54 of column 12 read as follows: "yeast extracts with mineral glycopeptides and amino acids, such as selenomethionine or zinc glycopeptide ...". The

disclosed term of "mineral" also refers to the term "amino acid" if read in context. This is because the mineral in the term "zinc glycopeptide" is really "zinc", and the mineral in the term "selenomethionine" is "selenium". Therefore, the cited passage is clearly no evidence that the term "amino acid" includes the derivative "selenomethionine". Thus, Applicant respectfully maintain their position that the cited Hersh '791 fails to disclose or recognize the composition of the present invention, as further evidenced by the state of the art. Withdrawal of this rejection is respectfully requested.

Removal of the Rejection over Hillebrand '500

Hillebrand '500 also fails to describe at least one individual amino acid. Hillebrand '500 describes a method for regulating wrinkles or atrophy in mammalian skin using a composition comprising N-acetyl-L-cysteine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The teaching of Hillebrand '500 is to use N-acetyl-L-cysteine or a pharmaceutically acceptable salt thereof for regulating wrinkles (see column 1, penultimate paragraph). In the section entitled "Zinc Salts" from column 3, last paragraph to column 5, 1st paragraph, the cited Hillebrand '500 reference indicates that the compositions are rendered substantially

odorless by adding a zinc salt. The zinc most likely removes odors by complexing with malodorous H<sub>2</sub>S, which may be formed in trace amounts as the active compound decomposes (see column 3, lines 56 to 62). Similar to Hersh '791, Hillebrand '500 does not describe any composition comprising an individual amino acid. N-acetyl-L-cysteine is an amino acid derivative (see the present specification at page 7, lines 17 and 18). Furthermore, Hillebrand '500 does not teach a combination of an individual amino acid and zinc oxide and/or inorganic peroxide. In column 7, penultimate paragraph of Hillebrand '500, there is a list of compounds disclosed, with "soybean saponins" being one in this list with a multiplicity of other compounds. Nothing in Hillebrand '500 points particularly to the group of secondary plant substances. Moreover, nothing in Hillebrand '500 points to any improving effects of a composition comprising an individual amino acid, zinc oxide and/or inorganic peroxide and a secondary plant substance (SPS). Further, there is no hint in Hillebrand '500 that by the specific combination of components of the present invention health improving substances, particularly SPS's, can be infiltrated better into the cell.

Thus, Applicant submits there is no motivation for a person of ordinary skill in the art to replace the amino acid derivative in an example of Hillebrand '500 by any individual amino acid and, in

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addition thereto, add SPS in a pharmaceutically effective amount. It should be noted that the Examiner did not provide any evidence supporting the allegation that the person of ordinary skill would have a reasonable expectation of success by doing this since Hillebrand '500 is absolutely silent concerning any effects of a combination of amino acid, zinc oxide and SPS. Therefore, Hillebrand '500 cannot render obvious the instant invention because Hillebrand '500 fails to disclose the elements of the instant invention. Accordingly, withdrawal of the rejection over Hillebrand '500 is warranted and respectfully requested.

***Request for Interview with Applicant's Representative***

As mentioned above, Applicant respectfully requests an Interview with the Examiner, and further requests such Interview take place before issuance of the next Office Action. Applicant believes the Interview would advance prosecution of this application. Applicant also requests that the next Office Action be non-Final.

***Conclusion***

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus,

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Applicant respectfully requests that a timely Notice of Allowance issue for the present case.

If any questions remain regarding the above matters, or in efforts to advance prosecution, please contact Applicant's representative, Eugene T. Perez (Reg. No. 48,501), in the Washington metropolitan area at the phone number listed below.

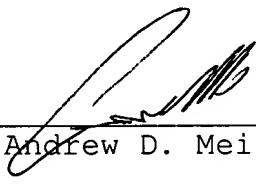
Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition for a two (2) month extension of time for filing a response in connection with the present application. The required fee of \$215.00 (small entity) is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

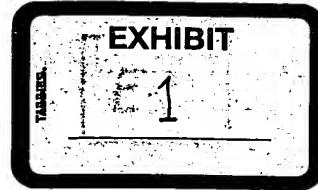
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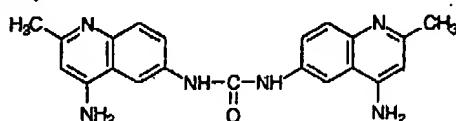
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## Aminopyrin

164

Aminopyrin s. Aminophenazon.

Aminoquinurid.



Internat. Freiname für *N,N'*-Bis-(4-amino-2-methyl-6-chinolyl)-harnstoff,  $C_{21}H_{20}N_6O$ ,  $M_R$  372,43, Zers. bei 255 °C. Es wurde als Mund-Antiseptikum 1934 von I. G. Farben patentiert u. ist in Kombination mit Tetracain Hydrochlorid von Hermal (Herviros®) im Handel. - *E* = *F* aminoquinuride - *I* amminoquinuride - *S* aminoquinurida

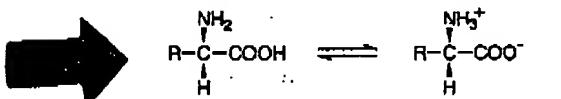
Lit.: Hager (S.) 7, 155-157. - [CAS 3811-56-1]

**Aminosäure-Austausch.** Austausch einzelner Aminosäuren in einem Protein. Der Austausch kann auf genet. Ebene durch eine \*Punktmutation (z. B. gezielt durch \*site-directed-Mutagenese) hervorgerufen werden. Durch Austausch eines Nucleotids in einem Codon kann bei der \*Translation eine andere Aminosäure eingebaut werden. Je nach Lage u. Eigenschaften der ausgetauschten Aminosäure innerhalb des Proteins ergeben sich unterschiedlich starke Auswirkungen auf seine Funktion.

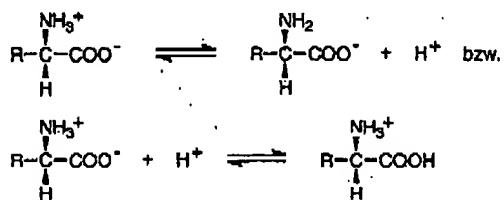
Auch fertige Proteine od. Peptide können durch A.-A. gezielt verändert werden. Ein Beisp. mit industriellem Nutzen ist die Abspaltung der C-terminalen Aminosäure Alanin aus Schweine-Insulin mittels Trypsin. Diese wird im Folgeschritt durch Threonin ersetzt, um Human-Insulin zu erhalten. - *E* aminoacid exchange - *F* échange d'acides aminés - *I* scambio degli amminoacidi - *S* intercambio de aminoácidos

Lit.: Oxender u. Fox (Hrsg.), Protein Engineering, New York: A. R. Liss 1987.

**Aminosäuren** (Aminocarbonsäuren). Bez. für \*Carbonsäuren mit einer od. mehreren Amino-Gruppen im Molekül. Im engeren Sinn versteht man darunter die 20 am Aufbau der Eiweißstoffe (\*Proteine) beteiligten (*proteinogenen*) u. in \*Nucleinsäuren kodierten, aber in der Natur auch frei vorkommenden L.-A. (L-2-Aminocarbonsäuren). In reinem Zustand sind sie farblose, krist. Stoffe, die in festem Zustand u. in neutralem wäss. Lsg. überwiegend als *innere Salze* (\*Zwitterionen) vorliegen, d.h. das chem. Gleichgewicht

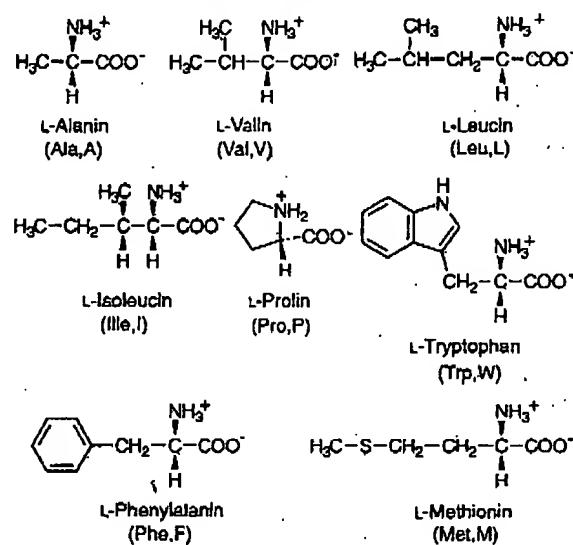


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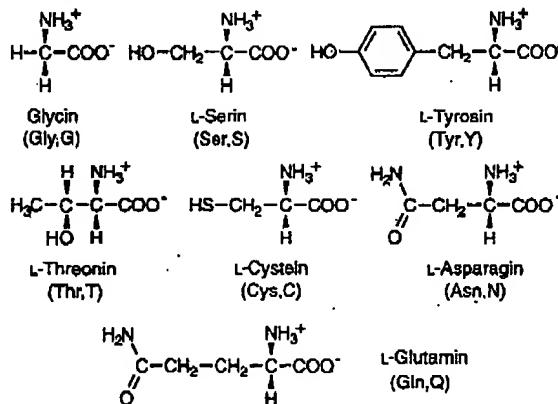


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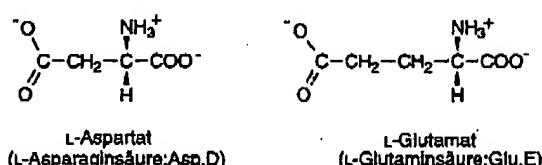
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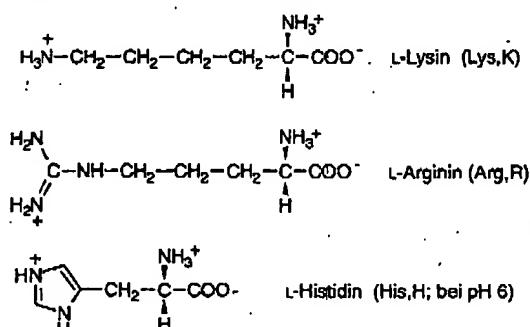


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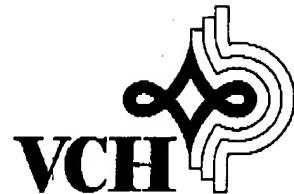
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# Amino Acids

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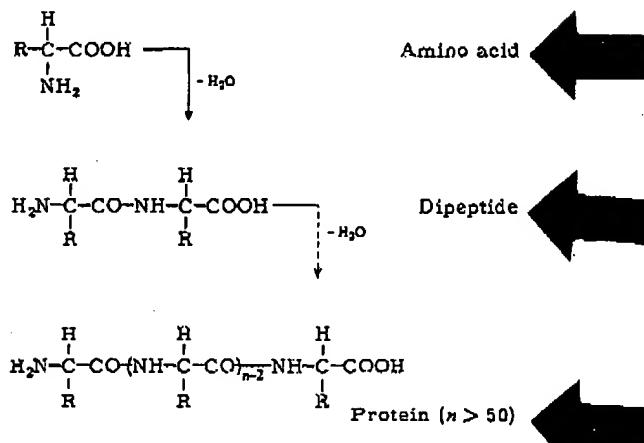
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## Introduction and History

The proteins, although they occur in an almost infinite variety, are composed of a relatively small number of basic building blocks, all  $\alpha$ -amino acids. In addition, the amino acids fulfill certain regulatory functions in the metabolism and are required for the biosynthesis of other functional structures. This review is limited, for the most part, to the protein-forming  $\alpha$ -amino acids, because they are by far the most widely distributed in nature and are of considerable economic interest.

The ca. 20 different  $\alpha$ -amino acids found in proteins are rather simple organic compounds, in which an amino group and a side chain (R) are attached alpha to the carboxyl function. The R

group may be aliphatic, aromatic, or heterocyclic and may possess further functionality. At present over 200 naturally occurring  $\alpha$ -



amino acids are known [1]–[3], [11]. Table 1 (pp. 58–59) shows the structures of the  $\alpha$ -amino acids found in proteins, where they occur exclusively as the L-enantiomers. D-Amino acids have been found only in the cell walls of some bacteria, in peptide antibiotics, and in the cell pools of some plants [6], [12], [13]. Table 2 lists some amino acids and derivatives that do not occur in proteins.

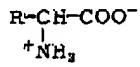
**History.** The history of amino acid chemistry began in 1806, when two French investigators, VAUQUELIN and ROBIQUET, isolated asparagine from asparagus juice. It was not until 1925 that SCHRYVER and BURTON isolated threonine from oat protein, the last discovered of the ca. 20 protein-forming amino acids. STRECKER synthesized alanine in 1850 from acetaldehyde and hydrogen cyanide. ESCHER established the hypothesis of essential amino acids. EMIL FISCHER discovered that the amino acids were building blocks of the proteins. ABBERHALDEN synthesized threonine from acrylic acid derivatives and methanol. ROSE et al. recognized threonine as the last of the eight essential amino acids. D,L-Methionine was produced industrially in Germany in 1948, and in 1956 L-glutamic acid was produced by fermentation in Japan.

**Origin of Amino Acids.** The first amino acids were probably produced on the earth more than  $3 \times 10^9$  years ago via "prebiotic synthesis" in the primordial atmosphere. The concept of prebiotic synthesis is based on laboratory experiments in which glycine, alanine, aspartic acid, glutamic acid, and other compounds were produced by the action of an electrical discharge on a simulated primordial atmosphere consisting of methane, hydrogen, water, and ammonia [14]. Since then, traces of amino acids have been detected in moon rocks, meteorites, and interstellar space.

## 1. Properties

### 1.1. Physical Properties and Structure

$\alpha$ -Amino acids are nonvolatile, white, crystalline compounds with no defined melting points. They are relatively stable on heating, generally decomposing at 250–300 °C. Both the low volatility and the thermal stability result from the low-energy dipolar structure (zwitterion, inner salt, betaine), which the amino acids assume in the solid state.



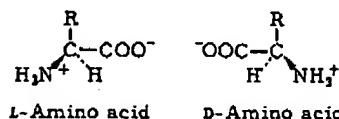
Evidence for this structure is provided by infrared and Raman spectra in which the bands typical of  $-\text{NH}_2$  and  $-\text{COOH}$  moieties are absent. Equilibrium in solution also lies almost exclusively on the side of the dipolar form; therefore, amino acids are insoluble in nonpolar solvents.

and usually not very soluble in polar ones. The only amino acids that exhibit any appreciable solubility in alcohol are proline and hydroxyproline. Solubility in water depends on the pH: the minimum is at the isoelectric point.

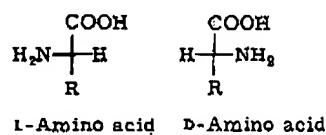
This solubility minimum at the isoelectric point is quite useful for purifying and recrystallizing amino acids. The analytical technique for separating amino acid mixtures by electrophoresis is based on the fact that a specific amino acid does not migrate in an electric field at its isoelectric point,  $pI$ , a physical constant for each amino acid.

The physical properties of the most important  $\alpha$ -amino acids are listed in Table 3.

**Stereochemistry.** With the exception of glycine, the simplest amino acid ( $R = H$ ), all natural  $\alpha$ -amino acids are chiral compounds occurring in two enantiomeric (mirror-image) forms.



The prefixes **L** and **D** express the absolute configuration about the  $\alpha$ -carbon atom by means of the formal stereochemical relationship to L- or D-glyceraldehyde, the reference substance introduced by EMIL FISCHER in 1891. In addition to the spacial representations shown above, the so-called Fischer projections are also universally recognized and used:



Polarimetric determination of the specific rotation  $[\alpha]_D$  can be used to differentiate between the two enantiomers and to check their optical purity. The molecular rotation  $[M']_D$  is less common:

$$[M]_D^e = \frac{M_r}{100} \cdot [a]_D^e$$

$M$ , molecular mass;  $t$ , temperature; D 589.3 nm (wavelength of the sodium D line)

Further methods for investigating the structure of amino acid enantiomers include the Cotton effect (change in molecular rotation as a function of the wavelength of plane-polarized light), optical rotational dispersion (reversal of the direction of the molecular rotation at the wavelength of the absorption maximum), and circular dichroism (differing absorption for left- and right-handed circularly polarized light). L-Amino acids exhibit a positive carbonyl Cotton effect, D-amino acids a negative one.

Isoleucine, threonine, and hydroxyproline contain two chiral carbon atoms each; therefore, they appear in four stereoisomeric forms. Cystine, which likewise contains two chiral carbons, has only three stereoisomers: L-, D-, and

nized clearly, and considerable growth can be predicted.

#### 4.3.1. Nutritive Agents

**Infusion Solutions.** Parenteral nutrition with L-amino acid infusion solutions is a well-established component of clinical nutrition therapy. A standard infusion solution contains the eight classical essential amino acids, the semi-essential amino acids L-arginine and L-histidine, and several nonessential amino acids, generally glycine, L-alanine, L-proline, L-serine, and L-glutamic acid.

Also available are special infusion solutions tailored to the requirements of particular groups, such as newborn infants, seniors, or patients with an extreme negative nitrogen balance. Solutions rich in the branched-chained amino acids leucine, isoleucine, and valine and poor in methionine and aromatic amino acids are available for liver-disease patients. Solutions containing only essential amino acids are available for kidney patients. Enzymatic protein hydrolysates, which were used as infusion solutions until a few years ago, have disappeared almost completely from the market. They were not available in the optimal composition, and there were often compatibility problems. Only pure, crystalline L-amino acids are used in modern infusion solutions. The solutions (up to 10%), which also contain electrolytes in addition to amino acids, are sterile and pyrogen-free.

The simultaneous administration of carbohydrates is necessary for optimal utilization of the amino acids. Glucose is normally a separate infusion. Some commercially available amino acid infusion solutions contain an energy source in the form of sugar alcohols (sorbitol, xylitol), which do not enter into a Maillard reaction with the amino acids.

Normally, parenteral nutrition is only practiced over a limited time. In principle, however, total parenteral nutrition over many years is possible. In such a case, all essential nutrients (unsaturated fatty acids, vitamins, and trace elements) must be provided.

**Elemental Diets.** Enteral nutrition is also a means of providing the essential nutrients [222]. Elemental diets, which were developed originally for the astronauts [223], contain chemically defined nutritive components. In addition to free amino acids the mixtures generally contain carbohydrates, fats, minerals, and vitamins in a combination adapted to the requirements. In many cases, elemental diets are used as an alternative and supplement to parenteral nutrition. They have high nutritional value and are totally resorbable. They are largely independent of the digestive function of the pancreas and reduce the intestinal bacteria flora. Amino acid elemental diets generally are used in cases of anatomic, functional, or enzymatic defects [224].

Formula diets based on peptides currently are gaining ground as an alternative to elemental diets based on L-amino acids. According to recent studies [225], short-chained peptides are resorbed rapidly via a peptide transport system in the gut, therefore in a process that is inde-

pendent of amino acid transport. Recently, compositions of nitrogen-free amino acid analogues (keto acids and hydroxy acids) have come into use for the special case of kidney insufficiency (chronic renal failure).

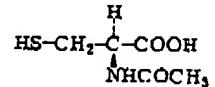
Elemental diets or formula diets are administered orally or via a nasogastric tube directly into the gastrointestinal tract.

#### 4.3.2. Therapeutic Agents

Many therapeutic agents are derivatives of natural or nonnatural amino acids. Examples are benserazide, captopril, and dextrothyroxine. They are described under keywords such as Spasmolytics, Blood Pressure Affecting Agents, or Thyrotherapeutic Agents. Only therapeutically useful amino acids and simple derivatives are treated here.

**Amino Acids and Salts.** The amino acids and their simple salts that are currently important therapeutic agents are compiled in Table 20. The proprietary names listed represent only a selection.

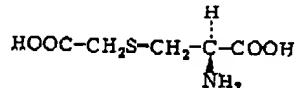
**N-Acetylcysteine** [616-91-1],  $C_5H_9NO_3S$ ,  $M_r$  163.2,  $mp$  109–110 °C,  $[\alpha]_D^{20} + 5^\circ$  ( $c = 3, H_2O$ ), is a mucolytic and secretolytic agent.



It is prepared by reaction of cysteine hydrochloride monohydrate with acetic anhydride in the presence of sodium acetate [226], [227].

**Trade names:** Fluimucetin (Inpharzam, FRG), Fluimucil (Inpharzam, FRG; Zambon, Italy), Mucolyticum "Lappe" (Lappe, FRG), Mucomyst (Allard, France; Mead Johnson, USA), Airbron, Parvolex (Duncan Flockhart, UK).

**Carbocisteine** (carbocysteine) [638-23-3], S-carboxymethyl-L-cysteine,  $C_5H_9NO_4S$ ,  $M_r$  179.2,  $mp$  204–207 °C (decomp.),  $[\alpha]_D^{20} - 34.0$  to  $-36.0^\circ$  ( $c = 10, H_2O$ ), is used to treat disorders of the respiratory tract associated with excessive mucus.



Synthesis involves S-alkylation of L-cysteine with chloroacetic acid in the presence of sodium hydroxide [228], [229].

# Hunnius Pharmazeutisches Wörterbuch

E 3

EXHIBIT

3

8. Auflage

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von Artur Burger  
und Helmut Wachter

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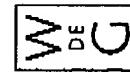
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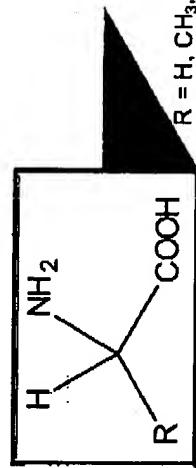


EXHIBIT

4

## Aminosäuren, Peptide, Proteine

Die Aminosäure ist der Grundbaustein jedes Eiweißkörpers oder Proteins (proteinogene Aminosäuren). Korrekt bezeichnet handelt es sich um  $\alpha$ -Aminocarbonsäuren, die eine  $\alpha$ -Aminogruppe ( $-\text{NH}_2$ ) und eine Carboxylgruppe ( $-\text{COOH}$ ) enthalten.

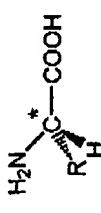


Die proteinogenen Aminosäuren haben eine gemeinsame Grundbauweise, unterschiedliche Aminosäuren unterscheiden sich nur durch ihre Seitenketten R.

## 12. Aminosäuren 01 2

### Aminosäuren, Peptide, Proteine

Beispiele für proteinogene Aminosäuren



$\alpha$ -Aminocarbonsäuren

Natürliche Aminosäuren sind chiral und besitzen S-Konfiguration

20 proteinogene Aminosäuren, natürlich vorkommende Aminosäuren, die zum Aufbau von Peptiden und Proteinen dienen

R	Trivialname	Abkürzung
$-\text{H}$	Glycin	Gly
$-\text{CH}_3$	Alanin	Ala
$-\text{CH}(\text{CH}_3)_2$	Vallin	Val
$-\text{CH}_2\text{OH}$	Serin	Ser
$-\text{CH}_2\text{CH}_2\text{OH}$	Tyrosin	Tyr
$-\text{CH}_2\text{CO}_2\text{NH}_2$	Asparagin	Asn
$-(\text{CH}_2)_4\text{NH}_2$	Lysin	Lys
$-\text{CH}_2\text{SH}$	Cystein	Cys
$-\text{CH}_2\text{COOH}$	Asparaginsäure	Asp
$-\text{CH}_2\text{CH}_2\text{COOH}$	Glutaminsäure	Glu

3

## 20 proteinogene Aminosäuren 3-Buchstaben-, 1-Buchstabsymbole

Gly	G	$\text{NH}_2\text{CH}_2\text{COOH}$
Ala	A	$\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}$
Vallin	V	$(\text{CH}_2)_4\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
Leucin	L	$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Isoleucin	I	$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Serin	S	$\text{HO}-\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
Threonin	T	$\text{CH}_3\text{CH}(\text{OH})-\text{CH}(\text{NH}_2)\text{COOH}$
Cystein	C	$\text{HS}-\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
Methionin	M	$\text{CH}_3\text{S}-\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
Prolin	P	$\text{CH}_2\text{NH}-\text{CH}(\text{NH}_2)\text{COOH}$
Phenylalanin	F	$\text{NH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Tyrosin	Y	$p\text{-HO}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Tryptophan	W	$\text{HOOC}-\text{CH}_2\text{NHC}(\text{H})-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Asparagin	N	$\text{NH}_2\text{CO}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Glutamin	Q	$\text{NH}_2\text{COO}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Asparaginsäure	D	$\text{HOOC}-\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$
Glutaminsäure	E	$\text{HOOC}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Arginin	R	$\text{HN}=\text{C}(\text{NH}_2)_2\text{NH}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Lysin	K	$\text{NH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$
Histidin	H	$\text{HOOC}-\text{CH}_2\text{NH}-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{COOH}$

4

## Die Aminosäuren werden eingeteilt in:

neutrale Aminosäuren: Glycin, Alanin, Vallin, Leucin, Isoleucin

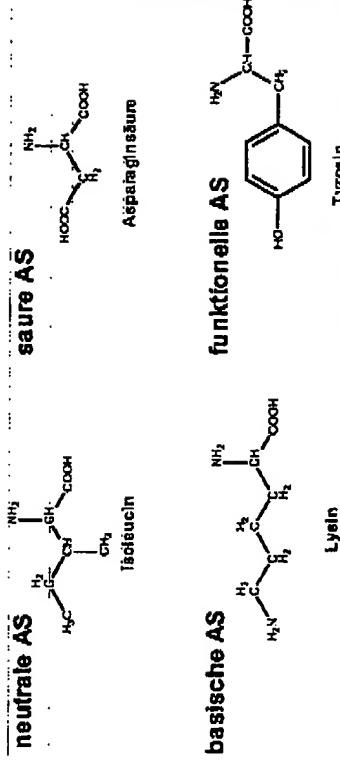
saure Aminosäuren: Asparaginsäure (Aspartat), Glutamin, Glutaminsäure (Glutamat), Glutamin

basische Aminosäuren: Lysin, Arginin

funktionelle und heterocyclische Aminosäuren: Serin, Threonin, Cystein, Cystin, Methionin, Phenylalanin, Tyrosin, Prolin, Tryptophan, Histidin

## 12. Aminosäuren 02 6

## Neutrale, saure, basische und funktionelle Aminosäuren



Glycin ist die einfachste Aminosäure. Alanin besitzt eine Methylgruppe ( $-CH_3$ ) an Stelle der  $-CH_2-$ . Valin, Leucin und Isoleucin zählen zu den neutralen Aminosäuren, deren Seitenketten bedingungen erfüllen, um polarisierte CH-Gruppen zu den  $\beta$ -Stoffwechsel zu den anderen Aminosäuren. Die Ammoniumsäure oder Iminosäure. Die Säureketten ist am des Stickstoff am der Aminogruppe gebunden. Die dadurch bedingte Ringstruktur hat einen großen Einfluss auf die dreidimensionale Struktur von Proteinen.

Phenylalanin gehört zu der Gruppe der aromatischen Aminosäuren. Bei Phenylalanin handelt es sich, wie auch bei Tyrosin, um eine stark hydrophobe Aminosäure. Sie zählt zu den für den Menschen essentiellen Aminosäuren.

Tryptophan ist eine aminosäure Aminosäure mit einem Indolring. Tryptophan ist eine hydrophobe Aminosäure und zählt zu den essentiellen Aminosäuren.

Niedrigan ist eine schwierige Aminosäure, das Schiefereatom ist in einer Triboethoxydialkylammonium-Zahl zu den für den Menschen essentiellen Aminosäuren. Das reaktive Oxyd mit seiner Triboethoxydialkylammonium-Zahl zu den für den Menschen essentiellen Aminosäuren. Durch Disulfidbildung zweier Cystathioneidektisch entsteht das Dimer Cystein, das eine große Rolle bei der dreidimensionalen Struktur der Proteine spielt.

Sein und Threonin sind Aminosäuren mit aliphatischen Hydroxygruppen. Sein ist im Pflanzenreich hydroxyliertes Alanin, Threonin ein hydroxyliertes Valin. Durch die Hydroxygruppe sind Sein und Threonin wesentlich polare und reaktiver als die anderen Aminosäuren.

Tyrosin ist eine aromatische Aminosäure und unterscheidet sich von Phenylalanin durch eine phenolische Hydroxygruppe. Sie ist ebenfalls als Phenylalanin und auch Tryptophan.

Asparagin und Glutamin sind Säureamide, der sauren Aminosäuren. Asparagin und Glutamin liegen beim physiologischen pH-Wert ungekettet vor und ziehen zu den hydrophilen Aminosäuren. Die Säureketten der Asparaginsäure und Glutaminsäure sind bei physiologischen pH-Werten negativ geladen. Lyzin ist deutlich bekannt als Protein Tyrosin und auch Tryptophan.

Arginin und Lysin enthalten jeweils eine starke positive Säureketten, die positive Seitenketten sind beim physiologischen pH-Wert stets negativ geladen. Lyzin auch die stärkste Basizität unter den Aminosäuren.

Die Proteinkette der Asparaginsäure und Glutaminsäure sind bei physiologischen pH-Werten negativ geladen. Arginin und Lysin enthalten jeweils eine starke positive Säureketten, die positive Seitenketten sind beim physiologischen pH-Wert stets negativ geladen. Lyzin zählt zu den für den Menschen essentiellen Aminosäuren. Die positive Seitenketten sind beim physiologischen pH-Wert stets negativ geladen. Proteine umgeleidet oder positiv geladen mit. Hartkohle findet sich häufig im aktiven Zentrum von Enzymen. Der Indizierung der Säureketten kann zwischen den kovalenten H- und Heteroatomen, ein wichtiger Unterschied bei der Katalyse von Lösung und Kondensation von Bindungen.

## Essentielle Aminosäuren

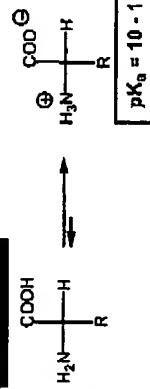
Für den Menschen gelten acht der zwanzig proteinogenen Aminosäuren als **essentiell**, da sie vom Körper nicht aufgebaut werden können und daher mit der Nahrung aufgenommen werden müssen.

Die essentiellen Aminosäuren sind Valin, Leucin, Isoleucin, Phenylalanin, Tryptophan, Methionin, Threonin und Lysin.

## 8

## Zwitterionische Struktur

$$pK_a = 2 \cdot 5$$

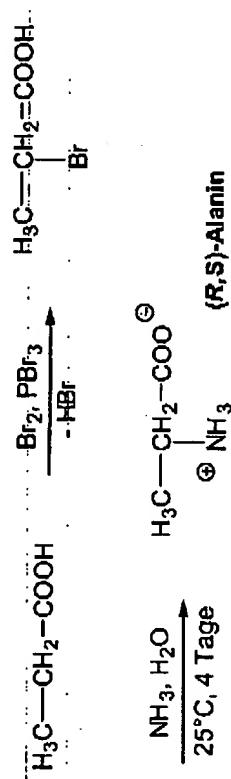


$$pK_a = 10 \cdot 11$$

## Isoelektrischer Punkt:

**Zahl der positiv geladenen Aminosäuremoleküle = Zahl der negativ geladenen**

## Synthese von Aminosäuren



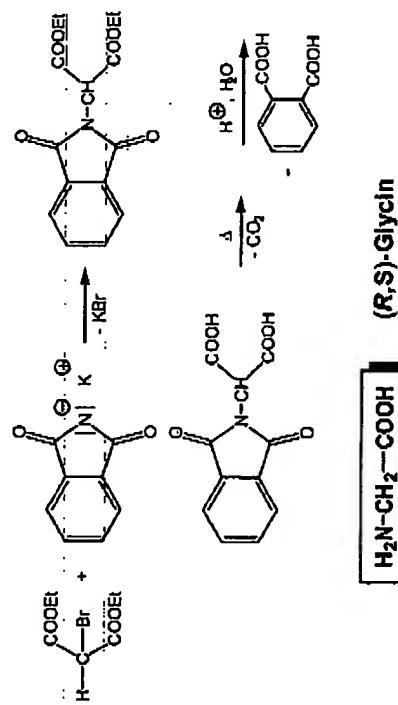
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## 12. Aminosäuren 03

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## Synthese von Aminosäuren

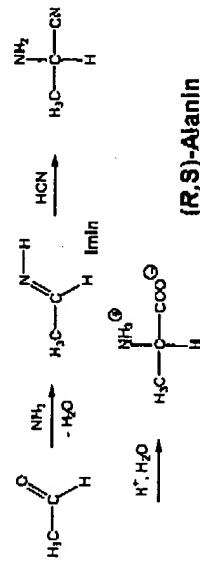
## Gabriel-Synthese von Glycin



11

## Synthese von Aminosäuren

## Strecker-Synthese von Alanin



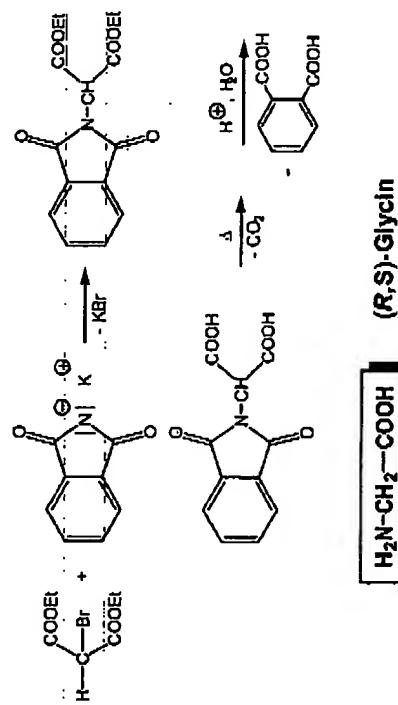
12

## 12. Aminosäuren 03

10

## Synthese von Aminosäuren

## Gabriel-Synthese von Glycin





EXHIBIT

E 5

# KLINISCHES WÖRTERBUCH

98,—

mit klinischen Syndromen  
und einem Anhang *Nomina Anatomica*

von

Professor Dr. med. Dr. phil.

Willibald Pschyrembel

Gegründet von Otto Dornblüth

Seiten.

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il253., um einen Anhang *Nomina Anatomica* erweiterte Auflage

Mit 2293 Abbildungen im Text

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## Amido-

42

## Amme

**Amido-:** s. Amino-.

**Amikrobiosis intestinalis** (de Rudder): Vollst. Fehlen v. Darmbakterien (Darmflora) insbes. nach Behandlg. mit Antibiotika.

**Amikronen:** Im Ultramikroskop nicht mehr erkennbare Teilchen (Durchmesser unter 1  $\mu$ ).

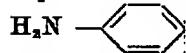
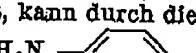
**Amimie:** Fehlen d. Mienenspiels (motor. A., atakt. A.) bzw. Nichtverstehen d. Mimik anderer (sensor. A.).

**Amindiabetes:** s. Aminosäurediabetes.

**Amine:** Abkömmlinge d. Ammoniaks, indem ein od. mehrere H-Atome durch Alkyl- od. Arylreste ersetzt sind. Primäre mit d. Gruppe  $-\text{NH}_2$  (Methylamin  $\text{CH}_3-\text{NH}_2$ ) entstehen durch Ersatz eines, sekund. mit d. Gruppe  $=\text{NH}$  (Dimethylamin  $(\text{CH}_3)_2\text{NH}$ ) durch Ersatz v. zwei, tert. mit  $\equiv\text{N}$  (Trimethylamin) durch Ersatz aller drei H-Atome. Quartäre Ammoniumbasen\* mit d. Gruppe  $\equiv\text{N}^+$  lassen sich v. Ammoniumhydroxyd  $\text{NH}_4\text{OH}$  ableiten. A., biogene (Guggenheim): Klasse von Stoffen, die durch Dekarboxylierung\* von Aminosäuren entstehen. Viele b. A. haben pharmakologische Wirkungen (z. B. Histidin\*  $\rightarrow$  Histamin\*), sind Teile von Coenzymen (z. B. Cystein\*  $\rightarrow$  Cysteamin\*) oder Vorstufen von Hormonen (5-Hydroxy-tryptophan  $\rightarrow$  Serotonin\*). Vgl. Monoaminooxydase, MAO-Hemmstoffe.

**Aminoazidurie** (acidum Säure, ούπον Harn): Angeb. od. erworbene Ausscheidung von Aminosäuren\* im Urin. Der Aminosäurespiegel im Serum schwankt ziemlich konstant um 4,2 mg%. Normalerweise werden nur 1—2% der aufgenommenen Aminosäuren im Urin ausgeschieden. Vgl. Hyperaminoazidurie.

**p-Aminobenzoësäure (PAB):**

  $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{COOH}$  Unentbehrlicher, noch in der Verdünnung von 10<sup>-11</sup> wirks. Wuchsstoff für Organismen, die Folsäure (s. Vitamin-B-Komplex) synthetisieren können (Bakterien). Das Enzymsystem, das PAB in die Folsäure einbaut, kann durch die Derivate d. Sulfanilamid   $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{SO}_2\text{NH}_2$  (= Sulfonamide\*) gehemmt werden (s. Antimetaboliten, Antivitamine). Ursache der selektiven Toxizität (Bakteriostase\* ohne Wirtsschädigung) d. Sulfonamide: Bei den Bakterien Unterbrechung der Folsäuresynthese; bei Tier u. Mensch ist Folsäure ein Vitamin, da Synthese nicht möglich. — Die PAB ist ferner d. Grundkörper e. Reihe v. Lokalanästhetika.

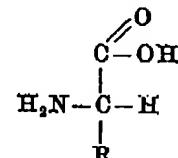
**Aminocapronsäure:** s. Epsilon-A.**Aminogalaktose:** syn. Galaktosamin\*.**Aminogruppe:**  $-\text{NH}_2$ .

**Aminosäurediabetes** (διαβήτις gehe hindurch) (Debré, de Toni, Fanconi 1936): syn. chronische Aminoazidurie; rezessiv erbliche Stoffwechselanomalie\* mit vermehrter Aminosäureausscheidung (Hyperaminoazidurie\*) auf Grund eines Enzymmangels (Phosphatase, Phosphorylase) in den Nierentubuli (proximale Abschnitte?).

Kann mit einem Phosphatdiabetes kombiniert auftreten als nephrotisch-glykosurischer Minderwuchs\* mit hypophosphatämischer Rachitis (s. u. Phosphatstörung).

**Aminosäuren:** Einfachste Bausteine der Eiweißkörper\*; Carbonsäuren, bei denen ein H durch eine Aminogruppe  $-\text{NH}_2$  ersetzt ist.

Die im Eiweißstoffwechsel wichtigen A. sind fast alle  $\alpha$ -A. u. L-A. Allgem. Formel:



Zwei A. bilden durch Peptidbindung ein Di-peptid, drei ein Tripeptid, bis zu 10 ein Oligopeptid, mehr als 10 ein Polypeptid, über 100 ein Protein. — Im Körper sind 25 Aminosäuren bekannt, davon sind 10 essentiell (Valin, Leucin, Isoleucin, Methionin, Threonin, Phenylalanin, Tryptophan, Histidin, Arginin, Lysin). 1. **Aliphatische A.:** Threonin, Isoleucin, Methionin, Valin, Leucin (Mono-A.); Lysin, Arginin (Di-A.). 2. **Aromatische A.:** Phenylalanin (Isozyklisch); Histidin, Tryptophan (heterozyklisch); ferner: glukoplastische A.: Können in d. Leber zu Glucose umgebaut werden, z. B. Glykokoll, Alanin, Arginin, Glutaminsäure usw.; vgl. Gluconeogenese; ketoplastische A.: Können in d. Leber Azetonkörper bilden, z. B. Leucin, Tyrosin, Isoleucin u. Phenylalanin.

**Aminosäuresequenz** (sequi folgen): Primärstruktur der Proteine\* (Aufklärung der ersten größeren Sequenz: Insulin, Sanger 1954).

**p-Amino-Salicylsäure (PAS):** s. Para-Amino-Salicylsäure.

**Aminosäureoxydasen:** Enzyme, die die oxidative Desaminierung von Aminosäuren katalysieren; Flavoproteide\*. Vgl. Eiweißstoffwechsel. Aus d. Aminosäure entsteht unter Abgabe von 2 H-Atomen eine Iminosäure, die dann zur Ketosäure u. Ammoniak hydrolysiert wird.

**Aminosidin:** syn. Paromomycin\*.

**Aminozucker:** Die Hydroxylgruppe e. Monosaccharids\* wird durch eine Aminogruppe ersetzt, z. B. Glucosamin\*, Galaktosamin\*. Bausteine hochmolekularer Naturstoffe, z. B. von Chitin, Hyaluronsäure.

**Aminurie:** Ausscheidg. v. Aminen i. Harn b. meist gleichzeitig. Aminoazidurie\* u. Di-aminurie\*. Bei Erkrankg. d. intermediären Stoffwechsels (z. B. b. Tb.).

E 6

# Remington's Pharmaceutical Sciences

A treatise on the theory and practice of pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities and services of the pharmacist as a member of the health team . . . A textbook and reference work for pharmacists, physicians, and other medical scientists

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### Liothyronine I 125 or I 131

Triiodothyronine I 125 (or 131);  $^{125}\text{I}$ -labeled T-3 (or 131);  
Liothyronine I 131 (Nuclear Consultants); Treotope (Squibb);  
Thiostat (Abbott).

Liothyronine labeled with either  $^{125}\text{I}$  or  $^{131}\text{I}$  by mild oxida-  
tion. For the structure of liothyronine, see page 909.

**Preparation**—By the exchange of crystalline synthetic  
hormone with  $^{131}\text{I}$  under carefully controlled conditions.  
Since such reactions always result in a mixture of products,  
purification must be effected by column and/or paper strip  
chromatography.

**Uses**—For *in vitro* evaluation of thyroid function.  $^{125}\text{I}$ -  
labeled T-3, added to an aliquot of the patient's serum, along  
with a source of secondary binding sites (Sephadex, ion-  
exchange resin, etc.), will become bound to binding sites on  
thyroxine-binding proteins (TBP) not occupied by thyroxine.  
 $^{125}\text{I}$ -labeled T-3 not bound to TBP becomes bound to  
the secondary binding sites in which form it is separated  
from the serum and measured, thereby providing an esti-  
mate of unoccupied binding sites on the TBP.

**Note**—Due to the high specific activity required, radia-  
tion damage can easily take place. This is in part pre-  
vented by the use of propylene glycol (50%) as a solvent.  
Packages should be refrigerated or even frozen during  
storage, and should not be used longer than 2 weeks.

**Note**—In making dosage calculations, correct for radioactive  
decay; for radiological constants, see Table II.

**Dose**—Not for internal use.

### Oleic Acid I 125 and I 131

#### Triolein I 125 and I 131

Oleotope I-125 (Squibb); Oleic Acid I 125 (Nuclear Consultants);  
Racoleic Acid-131 (Abbott); Oleotope and Oleotope Diagnostic (Squibb);  
Oleic Acid I 131 (Nuclear Consultants);  
Triolein I 125 (Nuclear Consultants);  
Kaolin-131 (Abbott); Triolein I 131 (Nuclear Consultants);  
Trioleotope (Squibb).

Oleic acid or triolein, which has been iodinated by mild  
oxidation of  $^{125}\text{I}$  or  $^{131}\text{I}$  to form iodostearic acid  $^{125}\text{I}$  (or  $^{131}\text{I}$ ) or  
triiodostearin  $^{125}\text{I}$  (or  $^{131}\text{I}$ ), respectively.

**Preparation**—Iodinated triolein is prepared by the ac-  
tion of iodine monochloride on the highly purified fat tri-  
olein, in a carbon tetrachloride solution. After removal  
of the solvent, and also all "free iodine," it is diluted with  
peanut oil to an activity of about 1 mCi/ml. The iodine  
bond is relatively stable in the digestive tract, but it is  
liberated as the molecule is metabolized in the blood stream  
and tissues.

Iodinated oleic acid is prepared in a similar manner and  
has similar properties.

**Uses**—As diagnostic agents for measuring fat absorption  
in suspected pancreatic disease or other gastrointestinal  
dysfunction. The use of these agents is based on the fact  
that the triolein, requiring pancreatic lipase for hydrolysis  
prior to passage through the gastrointestinal wall, is not ab-  
sorbed in cases of pancreatitis and cystic fibrosis, while the  
free acid, not requiring such hydrolysis, is taken up in the  
normal fashion. The assay for extent of absorption may be  
made on blood samples taken 2 to 8 hours after adminis-  
tration, or on 24- to 36-hour stool samples.

**Note**—In making dosage calculations, correct for radioactive  
decay; for radiological constants, see Table II.

**Dose**—Oral (capsules or oral solution), 25 to 50  $\mu\text{Ci}$ .

### Selenomethionine Se 75

Selenomethionine-75 (Diagnostic Isotopes); L-Selenomethionine-Se 75  
(Amersham Scarf).

An isotonic, sterile pyrogen-free solution of L-seleno-  
methionine containing an  $^{75}\text{Se}$  radioactive tag (7246-06-2).  
Selenomethionine is the selenium analog of the naturally  
occurring amino acid methionine. The general biochem-  
istry of selenomethionine and methionine are therefore very  
similar. See *Methionine* (page 964).

**Preparation**—Extracted from yeast grown on a sulfur-  
free medium to which trace amounts of sodium selenite,  
labeled with  $^{75}\text{Se}$ , have been added. After hydrolysis of  
the yeast, protein as  $^{75}\text{Se}$ -labeled amino acid is separated.

**Uses**—For scintigraphy of the pancreas and parathyroid  
glands. It has also been used to visualize the parotid and  
prostate glands.

**Note**—In making dosage calculations, correct for radioactive  
decay; for radiological constants, see Table II.

**Dose**—100 to 250  $\mu\text{Ci}$ .

### Sodium Chloride Na 22

Sodium Chloride Na 22 (Abbott; Nuclear Consultants)

A sterile, pyrogen-free solution of sodium chloride  $^{22}\text{Na}$   
[17112-21-9] suitable for injection.

**Preparation**—Cyclotron-produced by bombarding  $^{24}\text{Mg}$   
with deuterons. The reaction is  $^{24}\text{Mg}(d,\alpha)^{22}\text{Na}$ .

**Uses**—As an injection for the determination of circula-  
tion times, sodium space, and total exchangeable sodium.  
While the use of  $^{22}\text{Na}$  has certain advantages over the use of  
 $^{36}\text{Na}$  in medicine, its half-life of only 15 hours creates prob-  
lems of supply and the usual tracer dose of  $^{22}\text{Na}$  is well  
within the accepted tolerance level. Because  $^{22}\text{Na}$  emits  
positrons it can be detected readily by coincidence counting  
methods which combine the advantages of low background  
activity with high resolution.

**Note**—In making dosage calculations, correct for radioactive  
decay; for radiological constants, see Table II.

**Dose**—Intravenous, 5 to 10  $\mu\text{Ci}$ .

### Sodium Chromate Cr 51 Injection USP

Chromic acid ( $\text{H}_2\text{CrO}_4$ ), disodium salt; Chromotope Sodium (Squibb);  
Rachromate-51 (Abbott).

**Disodium chromate** ( $\text{Na}_2^{51}\text{CrO}_4$ ) [7775-11-3]. *Injection*  
**USP**: A sterile solution of radioactive  $^{51}\text{Cr}$  processed  
in the form of sodium chromate in water for injection. For  
those uses where an isotonic solution is required, sodium  
chloride may be added in appropriate amounts as provided  
under *Injections*, page 1461. The specific activity is not  
less than 10 mCi/mg of sodium chromate at the end of the  
expiration period. Other forms of radioactivity do not ex-  
ceed 10% of the total radioactivity.

**Preparation**—By neutron bombardment of enriched  
 $^{50}\text{Cr}$ .

**Description**—*Injection USP*: Clear, slightly yellow solution; pH be-  
tween 7.5 and 8.5.

**Uses**—A biological tracer to measure circulating red-cell  
volume, red-cell survival time, and whole-blood volume (red-cell  
mass and plasma volume). To tag erythrocytes, a sample  
of the patient's blood or of donor blood is mixed with a  
solution of  $\text{Na}_2^{51}\text{CrO}_4$  and allowed to remain until the isotope  
diffuses into cells (15 to 60 min). Once inside the cell, the  
bivalent chromate anion ( $\text{CrO}_4^{2-}$ ) is reduced to the tri-  
valent chromic cation ( $\text{Cr}^{3+}$ ), which firmly associates with  
the globin portion of the cell contents. The unbound  
chromium (in the plasma) is either reduced with ascorbic  
acid or removed by washing the cells. The treated blood  
or suspension of cells is then injected into the circulation,  
time allowed for complete *in vivo* mixing, and samples taken  
for scintillation counting. Red-cell or whole-blood volume  
is estimated by the radioisotope dilution method. Normal  
mean values for whole-blood volume obtained by the isotope  
method are  $65.6 \pm 5.95 \text{ mg/kg}$ .

Such tagged cells also provide an excellent means of studying  
red cell disappearance, as in hemolytic anemias and  
gastrointestinal bleeding. Platelets may also be labeled,  
though less effectively. For such purposes, it is essential  
that the specific activity be high—at least 5 to 15 mCi/mg.  
Such a solution, prepared by the peroxide oxidation of  $\text{Cr}-$   
 $\text{Cl}_3$ , is essentially colorless.

For greatest tagging efficiency, sterile vials are available  
containing a special formula ACD solution. The blood and  
chromate are added directly to these vials wherein tagging  
takes place.

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E7

## Neue Entdeckungen erweitern unsere Kenntnis über die Wichtigkeit von Selen

### Teil IV

#### Formen von Selen-Supplementen:

Die wirksamsten und sichersten Formen, unsere Ernährung mit Selen zu ergänzen, ist nicht die anorganische Salzform, sondern sind die organischen Formen Selenomethionin oder Selen-Hefe.

##### Selenomethionin:

Selenomethionine is a *protein*, Selenium containing amino acid.  
Selenomethionin ist eine gereinigte, Selen enthaltende Aminosäure. Es gibt keine Hefe in Selenomethionin. Es ist eine natürlich auftretende Komponente in bestimmten Lebensmitteln. Selenomethionin ist dem essentiellen Aminosäure-Methionin ähnlich, aber mit einem Selen-Atom statt einem Schwefel-Atom ausgestattet (Selenomethionine is comparable with the amino acid methionine, however has a selenium atom in place of the sulfur atom.)  
 Die Form von Selenomethionin, die der Körper verwenden kann, ist L-Selenomethionin (enthalten in SELEN, gebunden an Spirulina platensis). Dieses wird besser absorbiert und besser in die Körperkomponenten integriert als jede andere bekannte Form des Selens. Forscher, die anorganisches Selen mit DL-Selenomethionin verglichen, fanden, daß DL-Selenomethionin nicht so effektiv wie das anorganische Selen war (45). DL-Selenomethionin wird zu anorganischem Selen abgebaut und an den anorganischen Selen-Körperpool zurückgegeben. Dadurch beträgt die Bioverfügbarkeit nur 1/5 des L-Selenomethionin (31).

Prof. Richard A. Passwater hat dreißig Jahre lang verschiedene Formen des Selens bei seinen Tierstudien verwendet und herausgefunden, daß die Selen enthaltenden Aminosäuren (Selenomethionin und Selenocystein) und die methylierten Selenide gegenüber den anorganischen Formen von Selen (Selenit und Selenat) in bezug auf allgemeine Gesundheit, Langlebigkeit und Krebsverhinderung vorzuziehen sind.

Selenium containing amino acid (selenomethionine and selenocysteine)  
 In neuseeländischen Studien wurde herausgefunden, daß Selenomethionin mindestens zu 75 Prozent biologisch verfügbar ist, verglichen mit maximal 59 Prozent biologischer Verfügbarkeit bei der Einnahme von Natriumselenit. Die Blut-Selen-Spiegel stiegen mit Selenomethionin schneller und blieben konstanter als nach der Einnahme von Natriumselenit (30-32).

In einer finnischen Studie wurde nachgewiesen, daß Selenomethionin die Blut-Selen-Spiegel auch wesentlich stärker ansteigen ließ und diese Substanz länger im Blut verblieb als anorganisches Selen (33).

In einer 1984 durchgeführten MIT-Studie wurde festgestellt, daß organische Formen des Selens (Anm.: z.B. Selen/Spirulina) in der Lage sind, den Selen-

# Ullmann's Encyclopedia of Industrial Chemistry

Fifth, Completely Revised Edition

Volume A28:

Water to Zirconium and Zirconium Compounds

Editors: Barbara Elvers, Stephen Hawkins



(PER) because animal feeding tests were carried out at an assumed protein value higher than the true value. Much of the literature uses a PER value of 1.8 (cf. casein PER of 2.5).

Total yeast proteins are generally higher in lysine and deficient in sulfur amino acids, methionine, cysteine, and cystine as compared to cell-wall protein amino acid composition (see p. 462). The amino acid composition of yeasts resembles that of oil-seed proteins, particularly soy protein.

**Vitamins.** Most yeast species are unable to synthesize one or more vitamins and are dependent on external sources.

Yeast contains predominantly the vitamins of the B complex, and is thus an excellent source of B vitamins for human and animal nutrition.

Inactive dry yeast is frequently used as a vitamin supplement rather than as a source of protein in food formulations. Some dry yeast products are even fortified with vitamins such as B<sub>1</sub>, B<sub>2</sub>, and niacin to meet certain special requirements of vitamin tablet manufacturers. Although the daily requirements for most of the B vitamins are not fully met by the recommended yeast intake, their contribution to meeting the B complex vitamin requirements in the human diet is substantial. However, yeast does not provide vitamin C and fat-soluble vitamins such as A, E, K, and D. Nevertheless, dry yeast can function as a valuable vitamin source when used in combination with other food ingredients, as is generally the case with human diets.

Baker's yeast contains 7–10% ergosterol, mainly in the membranes. It serves as the precursor for vitamin D<sub>2</sub>. This conversion occurs when ergosterol is irradiated with ultraviolet light. However, this process is not economical since synthetic vitamin D<sub>2</sub> is less expensive. Baker's yeast does not contain 7-dehydrocholesterol, the precursor of vitamin D<sub>3</sub>.

**Minerals.** Yeasts take up substantial quantities of macro- and micronutrients from the surrounding growth medium. The mineral-ash content amounts to ca. 8% on a dry solid basis. Although the concentrations of potassium and phosphorus in dry yeast are higher than those of other elements such as Ca, Mg, and S, the mineral contributions made by an allowable daily serving of 20 g of dry yeast is minor considering the high mineral content in the bulk of an average human diet.

However, recent nutritional studies have shown that certain diets are deficient in some important trace elements. Supplementation of these diets with dry yeast has partially or wholly alleviated such dietary problems. Such inadequacies in the diet were later determined to be due to deficiencies of trace elements such as chromium, selenium, and molybdenum. Brewer's and baker's yeasts contain these elements in trace levels. Specially produced yeast products are now commercially available with higher levels of these micronutrients.

**Chromium.** In 1955 researchers reported that rats fed with certain nutritionally deficient diets showed impaired tolerance to blood glucose. The conditions were then reversed by supplementing the feed with brewer's yeast. It was later suggested that the active component responsible for reversing the glucose intolerance was an organic complex rich in chromium.

Diabetes, which is caused by glucose intolerance, can manifest itself in two ways. In juvenile diabetics, the pancreas fails to secrete insulin into the bloodstream. Those who are affected by another type of glucose intolerance begin to show symptoms in midlife. These patients secrete insulin into the bloodstream but cannot control their blood sugar level. It is possible to correct this problem by supplementing the diet with brewer's yeast. Findings have indicated the importance of another component besides insulin for the proper control of the blood sugar level. This active component, which is a trivalent chromium complex, is now referred to as glucose tolerance factor (GTF). Patients in the second category have GTF early in life, but tend to lose it with age, causing increased vulnerability to diabetes. It is suggested that GTF functions as a cofactor for insulin, thereby enhancing the binding of insulin to receptive sites on the membranes of insulin-sensitive tissues.

Other investigations showed a reduction in the level of cholesterol and triglycerides in the blood of humans supplementing their diets with brewer's yeast rich in GTF. However, further feeding studies are necessary to confirm the results before yeast rich in GTF could be recommended as a possible treatment for lowering blood sugar or curing lipid disorders.

**Selenium** has been recognized as an essential trace element for both human and animal nutrition. Recent surveys in some parts of Finland show that people with blood selenium less than 0.04 µg/L are three times more prone to heart

attacks than their counterparts with normal selenium levels. Also, in China a fatal heart disease in children known as Kaishan's disease is presently treated by fortifying the diet with sodium selenite.

The importance of selenium in animal nutrition is also well documented. A common disease in lambs, white muscle disease, is due to selenium deficiency. It can be cured by adding 0.05 ppm Se to the diet.

A diet containing Se at the levels approaching toxicity is effective in lowering the incidence of some types of cancer in animals. Research findings strongly suggest that certain types of cancer can be prevented by maintaining a proper level of Se in the diet.

Early feeding studies conducted with selenite or selenate salts as sources of Se showed that the uptake of Se was quite poor. In contrast, organically bound Se, such as selenomethionine found in some natural foods, is incorporated several times faster into the body tissue than inorganic Se.

Organically bound Se is now recognized as nutritionally important because of its ability to prevent some vitamin E deficiency disorders, at least in laboratory animals fed diets partially reduced in nucleic acids.

Reports, particularly from Finland, indicate that Se deficiencies can be corrected by supplementation with Se-rich yeasts.

There are several factors that restrict Se uptake by yeast under conventional batch propagation conditions primarily because of toxic effects of Se salts on yeast growth. However, a new procedure for the propagation of food-grade Se-rich yeast has been developed, based on the concept that, under conditions of sulfur deficiency, sulfur could be replaced by selenium in yeast. The growth medium is fed incrementally so that the Se concentration never reaches toxic levels. Under these conditions the yeast assimilates Se as a reaction to sulfur deficiency. Nutritional yeasts with an intracellular Se concentration of 1000 ppm are commercially available in the United States as dietary supplements.

**Lipids.** The lipid content of yeasts can vary between 4 and 7% (dry basis). About 1% can be extracted directly by solvents. The determination of total lipids requires acid hydrolysis prior to solvent extraction. Major constituents are fatty acid glycerides with a predominance of palmitic and oleic acids, sterols, and lipolipids.

**Carbohydrates.** Total carbohydrates account for about 30–35% of the yeast cell (dry basis). They consist mainly of carbohydrate storage compounds such as glycogen, the disaccharide trehalose, and the structural materials of the cell wall: the glucans and mannans. Level of fiber in whole baker's yeast cells is about 18% (dry weight basis).

### 3.2. Use of Yeast as a Major Protein Source

*Candida utilis* yeast was used as an important human diet supplement in Germany during World War II. Sulfite waste liquor, a byproduct of the paper pulp industry, and wood hydrolysates were used as raw materials. The large-scale production of yeasts on hydrocarbon substrates was found to be infeasible for economic and safety reasons.

For use as a major source of protein by humans the presence of nucleic acid is a serious obstacle; nucleic acid nitrogen accounts for about 10–15% of the total nitrogen of yeast cells. The intake of nucleic acid leads to elevated blood plasma levels of uric acid and may cause gout. Sources of nucleic acids in the diet are meat, particularly organ meat such as liver. Beer and possibly other fermented beverages also contain nucleic acids.

Search for methods is underway to reduce the level of nucleic acids or to remove them completely, since present methods are not economical. There is no need, however, for the removal of nucleic acids from yeast biomass for use in feed.

Yeast biomass in its inactive dried form is used widely as feed supplement. It is used in poultry rations and pig starter feeds. The use of brewer's and distiller's byproduct yeast in feed has been demonstrated. In countries that lack cheap sources of oil-seed meals (mainly soy bean meal), *Candida utilis* biomass is used extensively as a protein supplement. Live yeast cells in the form of active dried yeast or yeast culture are also used in the feed industry.

Yeast culture is produced by combining slurries of baker's yeast with cereal feed grains. The mash is incubated to permit yeast multiplication and fermentation. It is then dried at temperatures that preserve yeast viability.

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